ORIGINAL ARTICLE

ROLE OF INTRALESIONAL VITAMIN-D IN VIRAL WARTS

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Background: The study was to look for effectiveness of vitamin D-3 in cutaneous warts in comparison with cryotherapy at dermatology department of Pak Emirates Military Hospital Rawalpindi. It was a randomized control trial conducted at the Department of dermatology Pak Emirates Military Hospital Rawalpindi**.** Ten months, June 2019 to May 2020. M**ethods:** A total of 50 patients of cutaneous warts diagnosed by consultant dermatologist were included in the study. Patients were randomized into groups by lottery method. Group A received the Intralesional vitamin D 3 while Group B received cryotherapy. Comparison was made in both the groups regarding the response as complete or partial or no resolution of the wart. **Results** Out of 50 patients with cutaneous warts on any location of the body, 23 (46%) received intralesional vitamin D3 while 27 (54%) received cryotherapy as allocated treatment. Twenty-four (48%) patients were female while 26 (52%) were male. Planter warts 41 (82%) were the commonest type according to the site of warts followed by palmar 6 (12%). Application of chi-square test revealed that Vitamin D3 was statistically significantly related to complete resolution of warts as compared to cryotherapy (p-value<0.05). **Conclusion** Cutaneous warts were most commonly seen on the feet of the affected patients. They had a good response to both of the therapies but intralesional vitamin D3 emerged as more effective option of the two in terms of management of these cutaneous warts

Keywords Cryotherapy; Vitamin D3; Warts

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INTRODUCTION

Various dermatological conditions make up a huge chunk of diseases for which patients attend any health care facility.[1] These conditions may not be immediately life threatening but may have a negative impact on overall health related quality of life of the individuals.[2] Cutaneous warts have been one of those lesions which dermatologist commonly encounter in the outpatient departments all around the world. Statistics have not been different in out part of the world.[3]

Multiple etiological explanations have been given for cutaneous warts but evidence of relationship of viral infections with occurrence of these warts have been convincing.[4] These lesions have been affecting the skin of the patients for ages and multiple treatment modalities have been used to manage them. Few have become obsolete with time, but some have evolved and been quite effective.[5] New options have also been emerging with time and various trials still under process to test their efficacy and safety.[6]

Electrocoagulation, Topical keratolytic and cryotherapy have been used for long for treatment of cutaneous warts. Laser therapy has also been effective in this regard. Use of Intralesional vitamin D has been gaining popularity in recent past. Priya et al. did a study in India which was published last year with aim to assess the role of Intralesional Vitamin D3 in Recalcitrant Palmoplantar and Periungual Warts. More than 80 percent of their patients showed complete resolution of the warts while more than 90% of the periungual warts showed marked improvement after the four sessions of treatment. Injection pain and local swelling were the common side effects. They concluded that intralesional Vitamin D3 treatment has been an effective and safe option for the cutaneous warts.[7] Kavya *et al*. in 2017 did a similar study to evaluate efficacy and safety of vitamin D among patients suffering from cutaneous warts. Palmoplantar warts were the commonest lesions reported by them. They revealed that more than 2/3rd of their patients achieved complete resolution of warts. They found that recurrence was not uncommon in case of palmoplantar warts on long term follow up. No major side effects of the therapy were reported by them.[8] Taweel *et al*. discussed this phenomenon from a very interesting perspective. They studied the impact of smoking on therapeutic response of vitamin D among the patients with cutaneous warts. Their overall success rate in terms of complete resolution of warts was 40%. They concluded that smoking status and old age had significant impact on non-resolution of warts in response to vitamin D3 treatment.[9] Cutaneous warts may settle on their own as well, but it may take

months to years. Sometimes they may be source of stress to the individual due to cosmetic disfigurement and pain. A recent study published in Pakistan Armed forces medical journal by Riaz *et al.* which compared cryotherapy and zinc sulphate for management of the warts. Oral zinc sulphate emerged as a better option in their study.[10] We conducted this study to evaluate one of the novel options in comparison to cryotherapy so our main objective was to look for effectiveness of vitamin D-3 in cutaneous warts in comparison with cryotherapy at dermatology department of Pak Emirates Military Hospital Rawalpindi.

MATERIAL AND METHODS

This randomized control trial was conducted at the department of dermatology in Pak Emirates Military Hospital Rawalpindi from June 2019 to May 2020. Sample size was calculated by WHO Sample Size Calculator with population prevalence proportion of 96.7%.[11] Nonprobability Consecutive sampling technique was used to gather the sample for this trial. Patients of both genders with cutaneous warts on any area of body diagnosed by consultant dermatologist between the age of 18 and 60 years were included in the study.[12] Exclusion criteria were the patients with patients with infected warts or genital warts or those already receiving any treatment for the warts. Patients with other immunological or systemic conditions with mucocutaneous manifestations were also excluded from the study. Patients with history of allergy or intolerance to vitamin D3 or cryotherapy were also excluded from the trial. Patients who could not follow up or refused to become part of the trial were also not included in the study.

Ethical review board committee of the hospital was approached to get the ethical approval for this study with IREB letter no A/28/65/20. Written informed consent was taken from all the potential participants of this study before the start of study after complete description of the trial and clear understanding of both forms of treatment. They were told about their right to withdraw themselves at any time from this trial. Patients were divided into two groups A and B. Randomization was done via lottery method, so every patient had equal chances of falling into any of the two groups. Group A received the 0.2 ml of Vitamin D3 (15 mg/ml) into the base of each wart[13] while Group B received cryotherapy. Nitrous oxide liquid was used. Applicator tip was applied on the wart to freeze the epidermal tissue. Three freeze thaw cycles for 5 seconds each making a white rim of 1 mm around the wart. Application was performed according to the instructions for use.[14] Both treatments were carried out for four sessions two weeks apart. An independent clinician rated the response as complete resolution of the wart or partial or no resolution of the wart. Age, gender, duration of untreated wart and type of treatment were compared in patients with complete resolution and those with partial or no resolution of wart.

SPSS 24.0 was used to analyse the data for this study. Mean and standard deviation was calculated for age of the study participants and duration of untreated warts. Frequency and percentages were calculated for gender, number of patients which were included in both groups after the process of randomization and patients with complete, partial and no response to the treatment. Comparison in the groups was made with the help of chi-square test keeping *p*-value of less than or equal to 0.05 as significant.

RESULTS

After the application of exclusion and inclusion criteria, informed consent procedure and excluding the patients who were lost to follow up at the end of four sessions of designated treatment, 50 patients were included in the study. As randomization was not block, rather it was through lottery method so equal number of patients could not be ensured in both the groups. Out of 50 patients with cutaneous warts on any location of the body, 23 (46%) received intralesional vitamin D3 while 27 (54%) received cryotherapy as allocated treatment. Table-1 shows that 24 (48%) patients were female while 26 (52%) were male. Planter warts 41 (82%) were the commonest type according to the site of warts followed by palmar 6 (12%). Application of chi-square test (Table-2) revealed that Vitamin D3 was statistically significantly related to complete resolution of warts as compared to cryotherapy (*p*-value<0.05) while age, gender and duration of untreated warts had no significant association with complete resolution of warts among the target population (*p*-value>0.05).

Table-1: Characteristics of study participants (n=50)

Age (years)	
Mean±SD	32.45±5.166 years
Range (min-max)	18–58 years
Gender	
Male	26 (52%)
Female	24(48%)
Treatment received	
Cryotherapy	27(54%)
Vitamin D3	23 (46%)
Sites of warts	
Palmar	05 (10%)
Plantar	41 (82%)
Others	04 (8%)
Treatment response	
Complete resolution	38 (76%)
Partial resolution	08 (16%)
No resolution	04 (8%)

Table-2: Comparison of treatment modality and other factors between patients with complete resolution of warts and those with partial or no resolution

	Complete resolution	Partial or No resolution	p-value
Age			0.852
18-30 years	17 (44.7%)	05 (41.7%)	
>30 years	21 (55.3)	07 (58.3%)	
Gender			
No	18(47.4%)	06 (50%)	0.874
Yes	20 (52.6%)	06 (50%)	
Duration of untreated warts			
< 1 month	11 (28.9%)	06 (50%)	0.187
>1 month	27 (71.1%)	06 (50%)	
Treatment used			
Intralesional Vitamin D3	22 (57.9%)	01 (8.3%)	0.001
Cryotherapy	16 (42.1%)	11 (91.7%)	

DISCUSSION

Cutaneous warts may be considered as self-limiting and benign condition in most of the cases but still the cosmetic disfigurement, pain and discomfort may cause a negative impact on life of an individual.[15] Aman *et al*. in 2017 prepared a comprehensive draft of common skin conditions occurring in population of one of the biggest cities of Pakistan. They came up with the findings that viral infections including the cutaneous warts have been commonly encountered in dermatological and general physician out patient departments.[16] Few studies have been available regarding comparison of various treatment modalities for cutaneous warts in our population[10] but limited work has been done to assess the role of vitamin D3 in this perspective. We therefore conducted this trial to look for effectiveness of vitamin D-3 in cutaneous warts in comparison with cryotherapy at dermatology department of Pak Emirates Military Hospital Rawalpindi.

Shalduom *et al*. in 2020 conducted an interesting study comparing use of intralesional mumps, measles, rubella (MMR) vaccine and vitamin D3. They came up with the conclusion that both the treatment modalities had no statistical difference in any area may it be efficacy, adverse effects or the cost of reatment.[14]We did not compare cost as most of our patients have been entitled to free treatment and comparing the adverse effects was not the objective of our study. In terms of efficacy, Vitamin D3 emerged as a better option when compared to cryotherapy.

Raghukumar *et al*. in 2017 evaluated the role of intralesional vitamin D3 injections in the treatment of extragenital recalcitrant warts. They evaluated sixty patients and injected them 0.2–0.5 mL vitamin D3 solution (600,000 IU, 15 mg/mL). Around 96 percent of their patients had either complete or partial response with complete response in around 90%.[17] They did an experimental study and did not compare the drug under study with placebo or any other treatment option. Contrary to them we performed a RCT and compared vit D with cryotherapy. In terms of efficacy, we support their results as Vitamin D was very effective treatment and significantly more effective than cryotherapy.

Immune based treatments have also been tried and tested for cutaneous warts. Fathy *et al*. in 2019 did an effort in this regard and compared candida antigen immunotherapy with intralesional vitamin D3 and control group managed with saline. They divided sixty patients into three groups: Group I received intralesional vitamin D3, Group II intralesional Candida antigen, and Group III intralesional saline (control group). Injection was done every 3 weeks until clearance of warts or a maximum of three treatments. There was a statistically significant more reduction of warts numbers after treatment in Group I than in the other groups (p<.05). Group I showed better clinical response than Group II (p= .021). In both Groups I and II, clinical response was less favourable in patients with longer disease duration (p= .026). Intralesional vitamin D3 injection in multiple recalcitrant plantar warts emerged as a simple, safe, cost-effective treatment modality with minimal side effects, and superior results compared with intralesional injection of Candida antigen.[17] We did not compare Vitamin D3 with any immune based treatment but similar results were obtained when it was compared with cryotherapy which has been a standard treatment practiced for cutaneous warts.

As discussed earlier immune based and other treatment options have been tried for warts. An Egyptian study published in 202 by El-syed *et al*. compared 2% intralesional zinc sulphate with intralesional vitamin D3 and placebo (saline). After the regular four sessions they observed that both intralesional 2% zinc sulphate and vitamin D3 have been effective in treatment of plantar warts but zinc sulphate emerged as a much better option.[18] We did not compare zinc as cryotherapy was our comparison group therefore, we found Vitamin D3 as a better option.

There were few limitations in our trial which need to be mentioned. Sample size was small and from one military setting, therefore findings could not be generalized to local population. Systemic diseases were not controlled or made part of exclusion criteria which may have an impact on response of individual to the therapies. Adverse effects were not considered and made part of the objective because they may affect the adherence to the therapy. Future trials addressing these limitations may generate better results.

CONCLUSION

Cutaneous warts were most commonly seen of the feet f the affected patients. They had a good response to both of the therapies but intralesional vitamin D3 emerged as more effective option of the two in terms of management of these cutaneous warts

Conflict of interest: None by any of the authors

AUTHORS' CONTRIBUTION

ZZ: Data Collection and Article Writing
NAM: Statistical Analysis
SM: Helped in Article Writing
AM: Statistical Analysis
SO: Helped in Article Writing
KA: Data Collection
MM: Data Collection
AP: Data Collection
ZS: Helped in Article Writing

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